

AWARD NUMBER: W81XWH-16-1-0157

TITLE: Defining Hepatocellular Carcinoma Subtypes and Treatment Responses in Patient-Derived Tumorgrafts

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14. ABSTRACT Hepatocellular carcinoma (HCC) is the 6 th most common cancer and 3 rd leading cause of cancer-related death worldwide. We know that HCC subtypes exist because clear clinical, radiographic, and histological differences between patients with HCC are observed. In this study we proposed to investigate distinct subtypes of HCC using a mouse-human chimeric <u>Patient Derived Xenograft</u> (PDX) approach. So far, we have performed a large effort to implant 102 tumors from human HCC patients from Texas. We have established the protocol and the results have taught us that engraftment using a variety of transplantation techniques will result in a 25-30% engraftment efficiency for early stage surgical tumors. We have established 6 new human HCC PDX models that will be highly relevant for therapeutic and biological studies. These represent North American HCCs, including some patients with intermediate/advanced stage HCC, which is a unique resource for the field.						
15. SUBJECT TERMS HCC, patient derived xenografts, siRNA, mouse models of cancer.						
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The text of the report must include all sections addressed in the table of contents to include the following. **DO** include the bolded section headings, but **DO NOT** include the *italicized* descriptions of section contents in your submitted reports.

1. **INTRODUCTION:** Hepatocellular carcinoma (HCC) is the 6th most common cancer and 3rd leading cause of cancer-related death worldwide. In the US, its incidence has doubled over the past two decades due to the growing number of patients with hepatitis C virus (HCV) and/or non-alcoholic steatohepatitis (NASH) (El-Serag, 2004, 2012). We know that HCC subtypes exist because clear clinical, radiographic, and histological differences between patients with HCC are observed (Yopp et al., 2015). In this study we proposed to investigate distinct subtypes of HCC using a mouse-human chimeric Patient Derived Xenograft (PDX) approach. We aim to analyze and functionalize early and advanced stage HCC tumors with a large and representative cohort of patient derived xenograft (PDX) models. Our hypothesis is that HCC is poorly understood because tissue has been obtained from early HCC but not advanced cases. Biological subclasses of HCCs that behave differently in terms of natural history, prognosis and treatment response have not been categorized and/or functionally analyzed. Our team will use human-mouse PDX models to uncover novel biology and establish a platform to study experimental therapeutics.

2. **KEYWORDS:** HCC, patient derived xenografts, siRNA, mouse models of cancer.

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Specific AIM 1: Determine if early vs. advanced HCCs have distinct cell-intrinsic biology in PDX engraftment assays

Major Task 1: Expand and characterize PDX models derived from surgical and biopsy HCC specimens (ongoing).

Major Task 2: Compare biological and genetic features (stage, survival, progression) of early vs. non-early HCCs (ongoing).

Specific AIM 2: Determine the efficacy of small RNA therapeutics against the LIN28B/LET-7 pathway in PDXs activating this oncogenic pathway

Major Task 1: Identify and deliver small RNAs to target PDX populations (ongoing).

Major Task 2: Define response to small RNAs in target PDX populations (ongoing).

Specific AIM 3: Define targeted therapy responders with HCC-PDX patient avatars and use to identify predictive biomarkers

Major Task 1: Define PDX models that show partial response, stable disease, and progressive disease to targeted therapies

Major Task 2: Establish predictive biomarkers for response to treatment

- **What was accomplished under these goals?**

Specific AIM 1: Determine if early vs. advanced HCCs have distinct cell-intrinsic biology in PDX engraftment assays

Major Task 1: Expand and characterize PDX models derived from surgical and biopsy HCC specimens

Pre-task: Allow time to receive the regulatory approval for animal use (IACUC and DoD ACURO). This task was performed by Drs. Yopp, Singal, and Zhu. We obtained regulatory approval for the animal work in 11/2016.

Pre-task 2: Allow time to receive the regulatory approval for the Human Anatomical Substance use (IRB and DoD HRPO). This task was performed by Drs. Yopp, Singal, and Zhu. We obtained IRB approval in 11/2016.

Subtask 1: Continue to implant surgical HCC specimens in the subcutaneous space and livers of NSG mice. This task has been an ongoing task for the first year, and Drs. Yopp and Zhu are responsible for this work. Remarkably, we have now implanted 102 primary human HCC tumors into immunodeficient mice. This is a large number of patients and thus we can now make solid conclusions about the efficiency of PDX modeling for HCC. More than 30 of these have grown macroscopically in the primary transplant setting within 6 months. We define this as engraftment. Histologically, most of these are reflective of the primary HCC histology.

First we will discuss the cases that engrafted in NSG mice. Among the 9 NSG cases that engrafted, 4 grew in the setting of the mouse liver, 5 grew out from the subcutaneous space, and 1 grew out from both liver and SQ implantation. To stimulate an even higher rate of engraftment, we also surgically resected 30-40% of NSG liver at the time of tumor implantation in order to increase the growth factors that are being produced while the tumor is growing. In this setting, another 8 PDX tumors engrafted. 7 of these 8 grew out from subcutaneous implants, and 1 grew out from liver implantation. Most of these are also reflective of the primary HCC histology, but we found a few cases of lymphoma like histology, which is commonly seen in PDX experiments since the human lymphocyte contamination can proliferate into a tumor mass. For the hepatectomy experiments, we found that the ultimate rate of engraftment did not increase substantially, but the kinetics of engraftment did increase. We also implanted tumors into FRG recipient mice to stimulate engraftment. These mice represent a genetic model of hereditary tyrosinemia (Fah null) and have also been crossed to the Rag1 null and IL2gamma null immunodeficient background so that the mice are able to receive exogenous human cells. The diseased environment of this recipient model promotes the growth of HCCs. In this FRG transplant setting, we obtained 5 additional engrafted PDX tumors. Furthermore, we have 29 more ongoing PDX candidates that were either engrafted within 12 weeks and thus it is too soon to know the results or have not been harvested to assess tumor engraftment in liver. Overall, we have found that there is a good engraftment rate hovering around 25-35% but the HCCs from our patient population grow relatively slowly.

Subtask 2: Continue to implant 25 biopsy samples from intermediate and advanced HCC cases in the subcutaneous space and livers of NSG mice. This is the responsibility of Drs. Yopp, Singal, and Zhu. We have not implanted enough biopsy samples to make solid conclusions, in part because it is rarer for biopsies to be performed, and because there is often very little tissue obtained during biopsy procedures. The advantage of implanting biopsy samples is that there will be shorter warm ischemia waiting times than surgical HCC specimens before the implant. The disadvantage is the limited quantity and size of specimen that we can have. We are in the process of implanting more biopsy samples so that we can compare the engraftment rate of biopsy vs. surgical samples. So far we have 8 more ongoing biopsy PDX candidates that were implanted within 10 weeks, thus we do not yet know the ultimate results. We will continue implanting more and obtain more robust results over time.

Subtask 3: Harvest primary PDX tumors, establish PDX bank, and passage into additional NSG mice. This has been performed under the supervision of Drs. Yopp and Zhu. For all primary tumors that engrafted and that are passaged, we have collected tumor, snap frozen in 10% DMSO/FBS to make a tumor stock. At the same time, we re-implanted fragments of the tumor to additional NSG mice to see whether they can be passaged and how many passages they can be maintained, and will the PDXs maintain similar to their original patient tumor after several passages. For the 23 tumors successfully engrafted, we re-implanted all of them to another batch of recipient mice to see whether they can be passaged. Among them, there are 12 tumors that could be successfully passaged. Among these, 6 stopped after 3 to 5 passages and 6 of them are still growing

after more than 6 passaged. There are also 6 tumors that have been re-implanted within 12 weeks thus too soon to tell whether they are transplantable or not.

Subtask 4: Characterize tumor architecture, histology, growth, invasiveness, and paraneoplastic features of tumors that engraft, and determine if the grafts resemble or deviate from original tumors (surgical or biopsy specimens). Descriptively, we have found that most of the engrafted tumors have strong resemblance to the original tumors; however, we have yet to perform formal analyses to compare the two given insufficient numbers at this time. To examine the growth characteristics, further analysis of the growth rate of PDX tumors and original patient tumors will be required. We have collected the necessary clinical data associated with the patient tumors and will determine if there is a statistical correlation with engraftment and growth rate with increased samples size in year 2 and year 3. For example, doubling time on imaging will help to determine the growth rate, as will survival and AFP tests.

Subtask 5: Obtain genomic data from PDX grafts to determine if they resemble or deviate from original tumors (surgical or biopsy specimens). This is being performed under the supervision of Drs. Yopp, Singal, and Zhu. We have isolated RNA and genomic DNA from patient tumor samples and have performed some RNA-seq, and targeted-DNA sequencing for common cancer causing genes. This data has not yet been analyzed. We will aim to determine if there is conservation of RNA expression and mutations between patient and PDX samples. At the University of Michigan site we have been holding bi-monthly meetings with the University of Texas Southwestern site staff and the Ann Arbor VA site to discuss study progress.

Specific AIM 2 (Determine the efficacy of small RNA therapeutics against the *LIN28B/LET-7* pathway in PDXs activating this oncogenic pathway).

Subtask 1: Evaluate and optimize custom dendritic nanoparticle delivery to PDX tumors
This has been completed

We have experience using 5A2-SC8 lipid nanoparticles (LNPs) in the MYC transgenic liver cancer model (IV injection), peritoneal ovarian cancer PDXs (IP injection), orthotopic patient-derived pancreatic cancer PDXs (IV injection), and additional in vivo cancer models. Using Cy5.5 fluorescence tracking, we have found that LNPs are taken up into MYC tumors and PDX IP tumors. We have demonstrated reproducible survival benefit in the MYC model and the ovarian model, both of which are very aggressive. We have not yet tried many xenograft studies. So we do not know how well they will accumulate in HCC PDX xenografts after IV injection. Therefore, we will spike in a small amount of Cy5.5-siRNA into the LET-7 LNPs to assess delivery. Then we will image the whole mouse and see if the tumor is carrying the label or not to get an idea if the LNPs are getting into the tumor. To date, we have validated this approach and confirmed our ability to reliably detect the Cy5.5 fluorescence signal in a tissue, cell, and time specific manner. Thus, we are now in position to initiate these studies in the HCC PDX models.

Subtask 2: Formulate and optimize siRNA and microRNA containing dendritic nanoparticles to ensure that successful modulation of LIN28B and or LET-7 is achieved in PDX models.

Ongoing 5A2-SC8 synthesis, 90% completed with anticipated completion date of November

2017. We have been synthesizing more of the chemical lipids that compose the 5A2-SC8 LNPs. We have improved the isolation procedure using flash chromatography of the key cationic lipid, 5A2-SC8. As a result, chemical structure analysis using nuclear magnetic resonance (NMR) spectroscopy and mass spectroscopy indicates that the new batches of 5A2-SC8 are pure and likely more potent. Before “releasing” the batch, we will do in vivo efficacy experiments (siRNA against FVII) to verify hepatocyte potency. We have also included some tolerability studies (e.g. weight change and liver function analysis) to ensure reasonable toxicity.

Subtask 3: Define HCC PDX models that overexpress MYC or LIN28B and those that

suppress LET-7 family microRNAs

So far we only have 6 human PDX models that grow well, so we will proceed with subtask 3 for all of these lines. We hypothesize that LET-7 overexpression will be tumor suppressive even if the tumor has moderate levels of LET-7 microRNAs.

Subtask 4: Therapeutically deliver siRNAs or microRNAs in dendritic nanoparticles to mice harboring these PDX models

Previous work in our lab by Dr. Liem Nguyen has shown that the miRNA LET-7 is an important regulator of liver regeneration and liver cancer. This was demonstrated in both a mouse model over-expressing modified LET-7 as well as a liver-specific LET-7 knock-out mouse. Later work showed that delivery of a LET-7g mimic packaged into 5A2-SC8 LNPs could inhibit tumor growth and improve survival in a transgenic mouse model of aggressive liver cancer. These mice overexpress c-MYC in a liver specific manner, leading to rapid development of liver tumors upon doxycycline withdrawal. This work demonstrated the low toxicity and high efficacy of this lipid nanoparticle delivery system while simultaneously proving that exogenous miRNA could be delivered to target organs for therapeutic purposes.

Currently, we are performing a similar study in a different model of human liver cancer. Though our LET-7g mimic delivery system was very effective in the c-MYC mice, we want to show that our system is therapeutically relevant to and effective in human liver cancer and not just in a transgenic mouse model. To that end, we have xenografted human hepatocellular carcinoma (HCC) tissue subcutaneously into the flanks of immunodeficient NSG mice. We are using the same LET-7g mimic (vs. control miRNA) and the same lipid nanoparticle delivery system as in our previous study. We are injecting the mice and measuring the tumor size weekly. By calculating tumor volume and plotting growth curves of these patient-derived xenografts (PDX), we can assess for therapeutic efficacy of our LET-7g in this model. For 2 of the successfully growing PDX models, we are testing LET-7 microRNA therapy. Ultimately, we plan to do this experiment in all 6 of our established, rapidly growing PDX models. We are performing this in two ways. First, we implanted these tumors in the SQ space and are treating the mice with LET-7g packaged into lipid nanoparticles. Since we know that it is more difficult for these lipid nanoparticles to be delivered into SC tumors, we are also performing splenic transplantations of these tumors into FRG mice. Once these tumors spread and grow within the liver, we will again perform weekly LET-7 microRNA treatments with LNPs. This type of splenic implantation into FRG should form the basis for how we assess siRNA and microRNA therapies since this is 1. A more accurate way to make orthograft HCC models, and 2. Allows better delivery of these small RNAs. We will read out abdominal circumference and death as endpoints.

- **What opportunities for training and professional development has the project provided?**
§ *Nothing to report*
- **How were the results disseminated to communities of interest?**
§ *Nothing to report*
- **What do you plan to do during the next reporting period to accomplish the goals?**

We are in the process of addressing major task 2, where our goal is to compare biological and genetic features (stage, survival, progression) of early vs. non-early HCCs. Specifically, we are comparing biological features of the tumors that engraft vs. those that do not using tumor intrinsic data like histology, growth rates, and genomic features. We are still completing the genomic studies to survey the genetic landscape of PDX population that successfully engrafts vs. the ones that do not engraft. We will also need to assess patient clinical features such as etiology, stage, survival, and progression.

We have started to implant more biopsy samples from advanced cases. This is going to help us determine if engraftment and growth rates from these potentially more aggressive cases are altered. We will determine if there is a difference between PDX made from early surgical or more advanced biopsy specimens. We hope that this data together help us achieve our first milestone, which is to co-author manuscript on biology and genomics of HCC PDX models.

To initiate Specific AIM 3 (Define targeted therapy responders with HCC-PDX patient avatars and use predictive modeling to identify prognostic biomarkers), we are engaging drug studies in the 6 PDX models that are successfully growing. We will start with using Regorafenib, which is a new second line agent in HCC. This drug is used after patients progress or cannot tolerate first-line therapy, i.e. sorafenib. It would be important to know if there are subsets of HCCs that are more responsive to Regorafenib. These 6 PDX models will be established and then the mice will be treated with Regorafenib. Other drugs will be tested after these initial experiments.

4. IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**
 - § The major impact at this point is that we have performed a large effort to implant 102 tumors from human HCC patients from Texas. We have established the protocol and the results have taught us how efficient this process will be. We have established 6 new human HCC PDX models that will be highly relevant for therapeutic and biological studies. These represent North American HCCs, including some patients with intermediate/advanced stage HCC, which is a unique resource for the field.
 - § We have found that increasing the rate of engraftment with partial hepatectomy or mouse models of chronic liver disease helps to make the growth and engraftment of the tumors more efficient.
- **What was the impact on other disciplines?**
 - § "Nothing to Report."
- **What was the impact on technology transfer?**
 - § "Nothing to Report."
- **What was the impact on society beyond science and technology?**
 - § "Nothing to Report."

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**
 - § No changes at this time.
- **Actual or anticipated problems or delays and actions or plans to resolve them**
 - § No delays encountered.
- **Changes that had a significant impact on expenditures**

§ None.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
 - § None.
- **Significant changes in use or care of human subjects**
 - § None
- **Significant changes in use or care of vertebrate animals.**
 - § None
- **Significant changes in use of biohazards and/or select agents**
 - § None

6. PRODUCTS:

- **Publications, conference papers, and presentations**
Report only the major publication(s) resulting from the work under this award.
 - § Nothing to Report at this time.
- **Website(s) or other Internet site(s)**
 - § None at this time.
- **Technologies or techniques**
 - § These techniques have been described above and will be reported to the community when a manuscript is published.
- **Inventions, patent applications, and/or licenses**
None
- **Other Products**
 - § Data or databases: We continue to collect patient data in a clinical database.
 - § Biospecimen collections: We have a human HCC biospecimen and PDX collection.
 - § Research material: We have established live mice carrying human HCC PDXs.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name: Hao Zhu

Project Role: Lead PI

Researcher Identifier (e.g. ORCID ID): 0000-0002-8417-9698

Nearest person month worked: 12

Contribution to Project: Direct the project, design the experiments and objectives, organize personnel, report progress to the DOD.

Name: Lin Li

Project Role: Senior Research Associate

Researcher Identifier (e.g. ORCID ID): none

Nearest person month worked: 12

Contribution to Project: Implantation of HCC specimens, passage of engrafted PDXs, storage of PDX tumors, drug treatments, gene expression analysis of tumors.

Name: Daniel Siegwart

Project Role: Co-PI

Researcher Identifier (ORCID ID): 0000-0003-3823-1931

Nearest person month worked: 12

Contribution to Project: Co-planned and co-directed research activities. Worked on nanoparticle delivery optimization to liver tumors.

Name: Qiang Cheng

Project Role: Postdoctoral Researcher

Researcher Identifier (e.g. ORCID ID): none

Nearest person month worked: 9

Contribution to Project: Developed nanoparticle delivery carriers with an improved ability to deliver RNAs to the liver.

Name: Adam Yopp

Project Role: Co-PI

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 12

Contribution to Project: Design and conducted experiments, participated in co-PI conference calls to organize personnel and direct project.

Name: Min Zhu

Project Role: Senior Research Associate

Researcher Identifier (e.g. ORCID ID): none

Nearest person month worked: 12

Contribution to Project: Implantation of HCC specimens, passage of engrafted PDXs, storage of PDX engrafts. inventory of HCC samples, preparation of genomic DNA libraries from HCC samples, data analysis, etc.

Name: Amit Singal

Project Role: Co-PI

Researcher Identifier (e.g. ORCID ID): 0000-0002-1172-3971

Nearest person month worked: 12

Contribution to Project: Design experiments, performed sequencing, participated in co-PI conference calls to organize personnel and direct project.

Name: Xin Luo

Project Role: Co-Investigator

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 12

Contribution to Project: She is analyzing the RNA-seq and DNA mutations from HCC and PDX databases.

Name: Akbar K. Waljee

Project Role: Co-PI

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: Developing a data analytic plan

See below for a chart that details the hours worked by staff at the University of Michigan site on this project for Quarter 1 and Quarter 2.

Name	Role	Quarter 1 (Oct/2016-Dec/2016 = 13 weeks)	Quarter 2 (Jan/2017-March/2017 = 13 weeks)	Quarter 3 (April/2017 – June/2017 = 13 weeks)	Quarter 4 (July/2017 – Sept/2017 = 13 weeks)
Akbar Waljee	Site PI	7.8 hours total	7.8 hours total	7.8 hours total	7.8 hours total
Maria Hughes	Project Manager	0 hours total	80 hours total	28 hours total	28 hours total
Rachel Lipson	Data Manager	26 hours total	26 hours total	26 hours total	26 hours total
Amanda Ellis	RA	78 hours total	78 hours total	78 hours total	78 hours total

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

For Hao Zhu, the following grants have become active:

R01 DK111588-01A1 (Zhu)

NIH NIDDK

Title: Enhancing mammalian liver repair and regeneration

The major goals of this proposal are to understand the role of SWI/SNF complex components in liver disease and regeneration.

CPRIT New Investigator Award

Cancer Prevention and Research Institute of Texas (Zhu)

9/1/2012 – 8/31/2016

No Effort Required

\$455,000

The *Lin28-LET-7* pathway in liver cancer

The major goals of this project are to determine roles for *Lin28* and *LET-7* in liver cancer development. AIM 1 of this grant has been completed and published. AIM 2 involves testing *LET-7* therapeutic delivery in cancer models, and this is not discussed in the current R01.

For Amit Singal, the following grants have become active:

NIH R01CA12008-01A1 (PI: Singal)

07/01/2017-06/30/2022

3.0 calendar

Harms of Hepatocellular Carcinoma Screening in Patients with Cirrhosis

The goal of this proposal is to quantify HCC screening physical, financial, and psychosocial harms across 3 healthcare settings (academic tertiary care center, safety-net health system, and Veterans Affairs system).

For Daniel Siegwart, the following grants have become active:

I-1855 (Siegwart)

6/1/2017 – 5/31/2020

1.0 calendar

Welch Foundation

\$60,000

“Design and synthesis of activatable pH-responsive water soluble dyes for biomedical imaging”

The main objective of this proposal is to develop fluorescene probes capable of detecting cancer metastases.

RSG-17-012-01-CDD 07/1/2017-06/30/21 0.4 calendar
American Cancer Society (ACS) \$165,000
"A functional polyester library for enhanced and selective miRNA delivery into patient-derived lung cancer cells for advanced cancer therapy"
This grant will identify materials that can preferentially deliver miRNAs to cancer cells, but not to normal cells using normal/tumor matched-pair screening approach.

For Akbar Waljee, the following grants have become active:

Veterans Health Administration (Waljee PI) 4/1/17 – 12/31/21 3.6 cal
mo
HX-16-005

Advanced Prediction Models to Optimize Treatment and Access for Veterans With Hepatitis C
The purpose of this study is to lay the groundwork for risk-based treatment of CHC among non-cirrhotic Veterans in the Veterans Health Administration (VHA) by: (1) developing accurate, clinically relevant, and implementable risk prediction models; (2) engaging Veterans to develop consensus on how to implement risk-based treatment; and (3) evaluating the clinical and economic effects of risk-based treatment.

Role: PI

MIDAS Waljee (Partner-PI) 3/1/17-3/1/20 .3 cal
mo

From Big Data to Vital Insights: Michigan Center for Health Analytics & Medical Prediction (M-CHAMP)

The center will house a multidisciplinary team that will confront a core methodological problem that currently limits health research — exploiting temporal patterns in longitudinal data for novel discovery and prediction.

Role: Co-Investigator

- What other organizations were involved as partners?

§ Besides UTSW and Michigan, "Nothing to Report."

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** For collaborative awards, independent reports are required from **BOTH** the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.
 - **QUAD CHARTS:** If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report. **DO NOT RENUMBER PAGES IN THE APPENDICES.**

NOTES:

MARKING OF PROPRIETARY INFORMATION: Data that was developed partially or exclusively at private expense shall be marked as "Proprietary Data" and Distribution Statement B included on the cover page of the report. Federal government approval is required before including Distribution Statement B. The recipient/PI shall coordinate with the COR/GOR to obtain approval. **REPORTS NOT PROPERLY MARKED FOR LIMITATION WILL BE DISTRIBUTED AS APPROVED FOR PUBLIC RELEASE.** It is the responsibility of the Principal Investigator to advise the COR/GOR when restricted limitation assigned to a document can be downgraded to "Approved for Public Release." **DO NOT USE THE WORD "CONFIDENTIAL" WHEN MARKING DOCUMENTS. DO NOT USE WATERMARKS WHEN MARKING DOCUMENTS.**